Letter to the Editor

Ovalbumin content of 2010-2011 influenza vaccines

To the Editor:

Egg allergies affect an estimated 0.12% to 3.6% of the population.[1] Although exceedingly rare, some reports of anaphylaxis after immunization with the influenza vaccine in patients with egg allergy resulted in guidelines that make severe egg allergy a relative contraindication for immunization with these vaccines.[2]

The currently available practice parameter[3,4] for administration of influenza vaccines to patients with egg allergy recommends using a vaccine with known ovalbumin content of 1.2 μg/mL or less and administering it in 2 doses (10% of the dose followed in 30 minutes by the remaining 90%) or as a single dose without prior vaccine skin testing. This recommendation is partly based on a study by James et al[5] in 1998 that showed that 2-step dosing was safe, even in patients with a history of anaphylaxis to egg. No subjects experienced adverse reactions to vaccines containing as much as 1.2 μg/mL. Unfortunately, the specific egg protein content of any given year's influenza vaccines is not readily available.

Compared with reports[6] of influenza vaccines in the mid-1990s and early-2000s that contained up to 42 μg/mL ovalbumin, today's vaccines contain lower amounts, as seen last season.[7,8] Although some package inserts do publish the upper ranges of ovalbumin content, most of these ranges exceed the maximum level presumed safe in patients with egg allergy. Given this uncertainty, many allergists perform skin prick testing before vaccine administration, as recommended in the new guidelines on food allergy sponsored by the National Institute of Allergy and Infectious Diseases[2] and other sources. Emerging data suggest that skin testing to the vaccine might not be necessary or helpful and that the vaccine might be safe to administer in a single dose.[4,9] This, however, is with the caveat that the vaccines contain a low amount of ovalbumin.

Another concern with the vaccine is variability between lots. There have been previous reports of variability of ovalbumin content from year to year in a single manufacturer's vaccine.[5,6] However, there are limited data on lot-to-lot variability within a single influenza season. According to the US Food and Drug Administration (FDA), as of January 12, 2011, individual manufacturers have produced between 18 and 145 lots of influenza vaccine. It is important to analyze several lots from a single manufacturer to determine whether there is much variability between lots in a given season.

The goal of this study was to determine the level of ovalbumin content in the 2010-2011 FDA-approved influenza vaccines and determine the lot-to-lot variability within a manufacturer in a single season. Such information would allow providers to determine the safest vaccine administration protocol.

TABLE I. Ovalbumin content in 2009-2011 FDA-approved influenza vaccines

Brand name	Reference	Stated ovalbumin content (μg/mL)	No. of lots tested	Median ovalbumin content (μg/mL)‡	Range of ovalbumin content (μg/mL)‡	Mean ± SD ovalbumin content (μg/mL)	Coefficient of variation
Afluria	McKinney et al*		**5**	**0.056**	**0.026-0.084**	**0.052 ± 0.024**	**0.46**
	Waibel and Gomez[7]		3	0.020	0.018-0.021	0.020 ± 0.002	0.08
	Li et al[8]		NP	NP	NP	NP	NP
	Manufacturer†	≤2					
Fluarix	McKinney et al*		**1**	**0.004**	**NA**	**0.004**	**NA**
	Waibel and Gomez[7]		NP	NP	NP	NP	NP
	Li et al[8]		1	0.0126	NA	0.0126	NA
	Manufacturer†	≤0.1					
Flulaval	McKinney et al*		**4**	**0.058**	**0.047-0.088**	**0.063 ± 0.019**	**0.31**
	Waibel and Gomez[7]		NP	NP	NP	NP	NP
	Li et al[8]		1	0.091	NA	0.091	NA
	Manufacturer†	≤2					
Fluvirin	McKinney et al*		**5**	**0.048**	**0.040-0.080**	**0.0551 ± 0.017**	**0.32**
	Waibel and Gomez[7]		NP	NP	NP	NP	NP
	Li et al[8]		6	0.033	0.015-0.020	0.031 ± 0.012	0.37
	Manufacturer†	≤2					
Fluzone	McKinney et al*		**5**	**0.176**	**0.107-0.330**	**0.196 ± 0.086**	**0.44**
	Waibel and Gomez[7]		4	1.161	0.716-1.421	1.115 ± 0.299	0.27
	Li et al[8]		23	0.590	0.146-1.217	0.594 ± 0.262	0.44
	Manufacturer†	≤10					
FluMist (Live)	McKinney et al*		**5**	**0.00076**	**0.00066-0.00085**	**0.00076 ± 0.000072**	**0.09**
	Waibel and Gomez[7]		2	0.004	0.001-0.007	0.004 ± 0.004	1
	Li et al[8]		3	0.0007	0.0005-0.0084	0.0032 ± 0.0045	1.41
	Manufacturer†	≤1.2					

NA, Not applicable; *NP*, not performed.

*Current study: data from 2010-2011 seasonal flu vaccine.

†Per package insert, except Fluzone and FluMist per communication with manufacturer.

‡McKinney et al (boldfaced) and Waibel and Gomez ovalbumin values were measured by using the Alpha Diagnostic International commercial ELISA kit. Li et al ovalbumin values were measured by means of ELISA in the Mayo Clinic Laboratory.

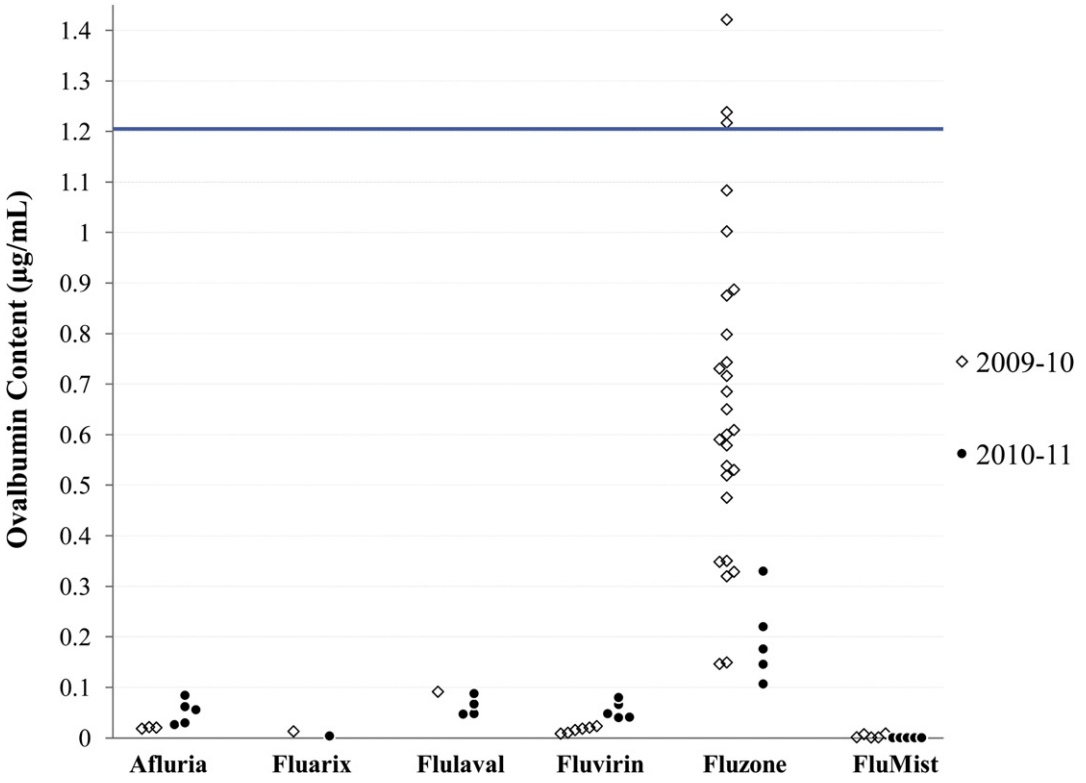

FIG 1. Ovalbumin levels reported for 2009-2010 *(open diamonds)* and tested in this study for 2010-2011 *(solid circles)*. Each *dot* represents the ovalbumin content of 1 lot. The *blue line* at 1.2 μg/mL represents the historical level of ovalbumin content below which all patients with egg allergy in the study by James et al[5] were safely vaccinated.

A commercial ovalbumin ELISA kit (Chicken Egg Ovalbumin; Alpha Diagnostic International, San Antonio, Tex) that has a sensitivity range of 0.5 to 4 ng/mL was used. Each vaccine lot was tested in duplicate. A total of 100 μL of each vaccine was added to predetermined wells that contained immobilized ovalbumin antibodies and incubated at room temperature for 1 hour, and then 100 μL of antiovalbumin enzyme conjugated to horseradish peroxidase was added. After a 30-minute incubation period, a stop solution was added, and the OD at 450 nm was measured. A standardized curve (0.5-4 ng/mL, $r^2 = 0.97$) was included for each plate. Vaccine dilutions ranged from 1:10 to 1:1000 to determine ovalbumin content by using the standardized curve.

The results of the tests are shown in Table I.[7,8] These data demonstrate that all of the tested 2010-2011 FDA-approved influenza vaccines contained much less than the stated ovalbumin content from the manufacturer (Fig 1).[5] The 3 injectable vaccines that reportedly contained 2 μg/mL or less (Afluria [CSL Biotherapeutics, Parkville, Victoria, Australia], Flulaval [ID Biomedical Corp of Quebec, Quebec City, Quebec, Canada], and Fluvirin [Novartis Vaccines and Diagnostics Ltd, Speke, Liverpool, United Kingdom]) actually contained about 40 times less at 0.052 to 0.063 μg/mL. Fluzone (Sanofi Pasteur, Swiftwater, Pa) has the highest reported ovalbumin content at 10 μg/mL or less and last season had some lots with greater than 1.2 μg/mL.[7,8] This season, none of the measured Fluzone lots had greater than 1.2 μg/mL ovalbumin, and the actual measured mean ovalbumin content was only 0.196 μg/mL. Fluarix (GlaxoSmithKline Biologicals, Dresden, Germany) has the lowest reported ovalbumin content of all the injectable influenza vaccines at 0.1 μg/mL or less, but given low production and unavailability from distributors early on, we were only able to test 1 lot. The actual measured ovalbumin content in this single lot of Fluarix was 0.004 μg/mL. The live attenuated intranasal vaccine FluMist (MedImmune, Gaithersburg, Md) contained the lowest measured ovalbumin content of all the influenza vaccines at 0.00076 μg/mL. All the 2010-2011 FDA-approved influenza vaccines measured in this study contained less than 1.2 μg/mL ovalbumin, which is depicted in Fig 1 and Table I, along with reported data from 2009-2010.

Comparing up to 5 lots from each manufacturer in the 2010-2011 season, the highest coefficient of variation was seen with Afluria at 46% and Fluzone at 44%. The coefficients of variation for Flulaval and Fluvirin were 31% and 32%, respectively. The lowest coefficient of variation was seen with FluMist at 9%. Because only 1 lot of Fluarix was measured, there are no data on variability this season for Fluarix.

Using the data from Waibel and Gomez[7] and Li et al[8] for the 2009-2010 season, the coefficient of variation was calculated for each brand and is also listed for comparison in Table I. In general, the coefficient of variation ranged from 27% to 46% between lots of injectable vaccine in both seasons, although Waibel and Gomez[7] reported data on 3 lots of Afluria with only 8% variation between lots. The live vaccine FluMist had inconsistent variability, ranging from 9% to 141%, although the absolute levels were extremely low (<0.001 μg/mL). It is important to note that different assays and laboratories might affect the variation seen with these measurements. For this reason, the data were not combined within or between seasons. The high coefficient of variation is reproducible across manufacturers.

In summary, although these data suggest that the 2010-2011 FDA-approved influenza vaccines measured in this study have lower ovalbumin content than last season and are well below 1.2 μg/mL, there is still uncertainty with lot-to-lot variability and variability from year to year and manufacturer to manufacturer. Measurement and reporting of the actual ovalbumin content of each manufacturer's vaccine would provide additional assurance that specific influenza vaccines do contain very low levels of ovalbumin. This could be done annually by the manufacturers, by academic centers, or by the Centers for Disease Control and Prevention with laboratory capabilities and resources available to provide this information.

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